Exhibit 10

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The designation on the cover of this publication, "USP NF 2007," is for ease of identification only. The publication contains two separate compendia: *The United States Pharmacopeia*, Thirtieth Revision, and the *National Formulary*, Twenty-Fifth Edition.

THE UNITED STATES PHARMACOPEIAL CONVENTION
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SIX-MONTH IMPLEMENTATION GUIDELINE

Beginning with *USP30–NF25*, the *United States Pharmacopeia–National Formulary* and its *Supplements* will become official **six months** after being released to the public. The *USP–NF*, which is released on November 1 of each year, will become official on May 1 of the following year.

This change was adopted to give users more time to bring their methods and procedures into compliance with new and revised *USP–NF* requirements.

The table below describes the new official dates. The 2006 *USP29–NF24*, and the *Supplements* and *Interim Revision Announcements (IRAs)* to that edition, will be official until May 1, 2007, at which time the *USP30–NF25* becomes official.

Publication	Release Date	Official Date	Official Until
USP30–NF25	Nov. 1, 2006	May 1, 2007	May 1, 2008 (except as superceded by *Supplements, IRAs,* and *Revision Bulletins*)
First Supplement	Feb. 1, 2007	Aug. 1, 2007	May 1, 2008 (except as superceded by *Second Supplement, IRAs,* and *Revision Bulletins*)
Second Supplement	June 1, 2007	Dec. 1, 2007	May 1, 2008 (except as superceded by *IRAs* and *Revision Bulletins*)
USP31–NF26	Nov. 1, 2007	May 1, 2008	May 1, 2009 (except as superceded by *Supplements, IRAs,* and *Revision Bulletins*)

IRAs will continue to become official on the first day of the second month of the *Pharmacopeial Forum (PF)* issue in which they are published as final. For instance, *IRAs* published as final in the May-June *PF* (issue 3) will become official on June 1. This table gives the details of the *IRAs* that will apply to *USP29–NF24* and *USP30–NF25*.

*IRA**	Release Date	Official Date	Revises
Jan. 1, 2007 *IRA, PF* 33(1)	Jan. 1, 2007	Feb. 1, 2007	*USP29–NF24* and its *Supplements*
Mar. 1, 2007 *IRA, PF* 33(2)	Mar. 1, 2007	April 1, 2007	*USP29–NF24* and its *Supplements*
May 1, 2007 *IRA, PF* 33(3)	May 1, 2007	June 1, 2007	*USP30–NF25*
July 1, 2007 *IRA, PF* 33(4)	July 1, 2007	Aug. 1, 2007	*USP30–NF25* and *First Supplement*
Sept. 1, 2007 *IRA, PF* 33(5)	Sept. 1, 2007	Oct. 1, 2007	*USP30–NF25* and *First Supplement*
Nov. 1, 2007 *IRA, PF* 33(6)	Nov. 1, 2007	Dec. 1, 2007	*USP30–NF25* and its *Supplements*
Jan. 1, 2008 *IRA, PF* 34(1)	Jan. 1, 2008	Feb. 1, 2008	*USP30–NF25* and its *Supplements*
Mar. 1, 2008 *IRA, PF* 34(2)	Mar. 1, 2008	April 1, 2008	*USP30–NF25* and its *Supplements*

*NOTE—Beginning January 1, 2007, USP will cease identifying *IRAs* numerically (*First, Second,* etc.) and instead will designate them by the date on which they are published.

Revision Bulletins published on the USP website will continue to become official immediately upon publication, unless the *Revision Bulletin* specifies otherwise.

General Chapters, monographs, or monograph revisions that contain a specific official date shall continue to become official upon such specified date, which supercedes the general official date for the publication.

For more information about the change in official dates, please visit the USP website at http://www.usp.org.

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temperature different from 25°, filled pycnometers must be brought to the temperature of the balance before they are weighed. Subtract the tare weight of the pycnometer from the filled weight.

The specific gravity of the liquid is the quotient obtained by dividing the weight of the liquid contained in the pycnometer by the weight of water contained in it, both determined at 25°, unless otherwise directed in the individual monograph.

METHOD II

The procedure includes the use of the *Oscillating transducer density meter.* The apparatus consists of the following:

- a U-shaped tube, usually of borosilicate glass, which contains the liquid to be examined;
- a magneto-electrical or piezo-electrical excitation system that causes the tube to oscillate as a cantilever oscillator at a characteristic frequency depending on the density of the liquid to be examined;
- a means of measuring the oscillation period *(T),* which may be converted by the apparatus to give a direct reading of density or used to calculate density by using the constants *A* and *B* described below; and
- a means to measure and/or control the temperature of the oscillating transducer containing the liquid to be tested.

The oscillation period is a function of the spring constant *(c)* and the mass of the system:

$$T^2 = \left(\frac{M}{c} + \frac{\rho \times V}{c}\right) \times 4\pi^2$$

where ρ is the density of the liquid to be tested, M is the mass of the tube, and V is the volume of the filled tube.

Introduction of two constants $A = c/(4\pi^2 \times V)$ and $B = M/V$, leads to the classical equation for the oscillating transducer:

$$\rho = A \times T^2 - B$$

The specific gravity of the liquid is given by the formula:

$$\rho_{(L)} / \rho_{(W)}$$

where $\rho_{(L)}$ and $\rho_{(W)}$ are the densities of the liquid and water, respectively, both determined at 25°, unless otherwise directed in the individual monograph.

Calibration—The constants *A* and *B* are determined by operating the instrument with the U-tube filled with two different samples of known density (e.g., degassed water and air). Perform the control measurements daily, using degassed water: the results displayed for the control measurement using degassed water do not deviate from the reference value ($\rho_{25} = 0.997043$ g/cm^{-3}) by more than its specified error. Precision is a function of the repeatability and stability of the oscillator frequency. Density meters are able to achieve measurements with an error on the order of 1×10^{-3}g/cm^{-3} to 1×10^{-5}g/cm^{-3} and a repeatability of 1×10^{-4}g/cm^{-3} to 1×10^{-6}g/cm^{-3}. For example, an instrument specified to $\pm 1 \times 10^{-4}$g/cm^{-3} must display 0.9970 ± 0.0001 g/cm^{-3} in order to be suitable for further measurement, otherwise a readjustment is necessary. Calibration with certified reference materials should be carried out regularly.

Procedure—Using the manufacturer's instructions, perform the measurements using the same procedure as for *Calibration.* If necessary, equilibrate the liquid to be examined at 25° before introduction into the tube to avoid the formation of bubbles and to reduce the time required for measurement. Factors affecting accuracy include the following:

- temperature uniformity throughout the tube,
- nonlinearity over a range of density,
- parasitic resonant effects, and
- viscosity, if the oscillating transducer density meters used do not provide automatic compensation of sample viscosity influence.

⟨846⟩ SPECIFIC SURFACE AREA

INTRODUCTION

The specific surface area of a powder is determined by physical adsorption of a gas on the surface of the solid and by calculating the amount of adsorbate gas corresponding to a monomolecular layer on the surface. Physical adsorption results from relatively weak forces (van der Waals forces) between the adsorbate gas molecules and the adsorbent surface of the test powder. The determination is usually carried out at the temperature of liquid nitrogen. The amount of gas adsorbed can be measured by a volumetric or continuous flow procedure.

BRUNAUER, EMMETT AND TELLER (BET) THEORY AND SPECIFIC SURFACE AREA DETERMINATION

Multipoint Measurement

The data are treated according to the Brunauer, Emmett and Teller (BET) adsorption isotherm equation:

$$\frac{1}{\left[V_a\left(\frac{P_o}{P} - 1\right)\right]} = \frac{C-1}{V_m C} \times \frac{P}{P_o} + \frac{1}{V_m C} \qquad (1)$$

P = partial vapor pressure of adsorbate gas in equilibrium with the surface at 77.4 K (b.p. of liquid nitrogen), in Pa,
P_o = saturated pressure of adsorbate gas, in Pa,
V_a = volume of gas adsorbed at standard temperature and pressure (STP) [273.15 K and atmospheric pressure (1.013×10^5 Pa)], in mL,
V_m = volume of gas adsorbed at STP to produce an apparent monolayer on the sample surface, in mL,
C = dimensionless constant that is related to the enthalpy of adsorption of the adsorbate gas on the powder sample.

A value of V_a is measured at each of not less than three values of P/P_o.

Then the BET value

$$\frac{1}{\left[V_a\left(\frac{P_o}{P} - 1\right)\right]}$$

is plotted against P/P_o, according to equation (1). This plot should yield a straight line usually in the approximate relative pressure range 0.05 to 0.3. The data are considered acceptable if the correlation coefficient, r, of the linear regression is not less than 0.9975; that is, r^2 is not less than 0.995. From the resulting linear plot, the slope, which is equal to $(C-1)/V_mC$, and the intercept, which is equal to $1/V_mC$, are evaluated by linear regression analysis. From these values, V_m is calculated as $1/(slope + intercept)$, while C is calculated as $(slope/intercept) + 1$. From the value of V_m so

determined, the specific surface area, S, in $m^2 \cdot g^{-1}$, is calculated by the equation:

$$S = \frac{V_m N a}{m \times 22\ 400} \quad (2)$$

N = Avogadro constant (6.023×10^{23} mol^{-1}),
a = effective cross-sectional area of one adsorbate molecule, in square meters (0.162 nm^2 for nitrogen and 0.195 nm^2 for krypton),
m = mass of test powder, in g,
22400 = volume, in mL, occupied by one mole of the adsorbate gas at STP allowing for minor departures from the ideal.

A minimum of three data points is required. Additional measurements may be carried out especially when nonlinearity is obtained at a P/P_o value close to 0.3. Because nonlinearity is often obtained at a P/P_o value below 0.05, values in this region are not recommended. The test for linearity, the treatment of the data, and the calculation of the specific surface area of the sample are described above.

Single-Point Measurement

Normally, at least three measurements of V_a, each at different values of P/P_o, are required for the determination of specific surface area by the dynamic flow gas adsorption technique *(Method I)* or by volumetric gas adsorption *(Method II)*. However, under certain circumstances described below, it may be acceptable to determine the specific surface area of a powder from a single value of V_a measured at a single value of P/P_o such as 0.300 (corresponding to 0.300 mole of nitrogen or 0.001038 mole fraction of krypton), using the following equation for calculating V_m:

$$V_m = V_a\left(1 - \frac{P}{P_o}\right) \quad (3)$$

The specific surface area is then calculated from the value of V_m by equation (2) given above.

The single-point method may be employed directly for a series of powder samples of a given material for which the material constant C is much greater than unity. These circumstances may be verified by comparing values of specific surface area determined by the single-point method with that determined by the multipoint method for the series of powder samples. Close similarity between the single-point values and multipoint values suggests that $1/C$ approaches zero.

The single-point method may be employed indirectly for a series of very similar powder samples of a given material for which the material constant C is not infinite but may be assumed to be invariant. Under these circumstances, the error associated with the single-point method can be reduced or eliminated by using the multipoint method to evaluate C for one of the samples of the series from the BET plot, from which C is calculated as (1 + *slope*/*intercept*). Then V_m is calculated from the single value of V_a measured at a single value of P/P_o, by the equation:

$$V_m = V_a\left(\frac{P_o}{P} - 1\right)\left[\frac{1}{C} + \frac{C-1}{C} \times \left(\frac{P}{P_o}\right)\right] \quad (4)$$

The specific surface area is calculated from V_m by equation (2) given above.

EXPERIMENTAL TECHNIQUES

This section describes the methods to be used for the sample preparation, the dynamic flow gas adsorption technique *(Method I)* and the volumetric gas adsorption technique *(Method II)*.

Sample Preparation

OUTGASSING

Before the specific surface area of the sample can be determined, it is necessary to remove gases and vapors that may have become physically adsorbed onto the surface after manufacture and during treatment, handling, and storage. If outgassing is not achieved, the specific surface area may be reduced or may be variable because an intermediate area of the surface is covered with molecules of the previously adsorbed gases or vapors. The outgassing conditions are critical for obtaining the required precision and accuracy of specific surface area measurements on pharmaceuticals because of the sensitivity of the surface of the materials.

The outgassing conditions must be demonstrated to yield reproducible BET plots, a constant weight of test powder, and no detectable physical or chemical changes in the test powder.

The outgassing conditions defined by the temperature, pressure, and time are chosen so that the original surface of the solid is reproduced as closely as possible. Outgassing of many substances is often achieved by applying a vacuum by purging the sample in a flowing stream of a nonreactive, dry gas or by applying a desorption-adsorption cycling method. In either case, elevated temperatures are sometimes applied to increase the rate at which the contaminants leave the surface. Caution should be exercised when outgassing powder samples using elevated temperatures to avoid affecting the nature of the surface and the integrity of the sample.

If heating is employed, the recommended temperature and time of outgassing are as low as possible to achieve reproducible measurement of specific surface area in an acceptable time. For outgassing sensitive samples, other outgassing methods such as the desorption-adsorption cycling method may be employed.

ADSORBATE

The standard technique is the adsorption of nitrogen of analytical quality at liquid nitrogen temperature.

For powders of low specific surface area (< 0.2 $m^2 g^{-1}$), the proportion adsorbed is low. In such cases, the use of krypton at the liquid nitrogen temperature is preferred because the low vapor pressure exerted by this gas greatly reduces error. The use of larger sample quantities, where feasible (equivalent to 1 m^2 or greater total surface area using nitrogen), may compensate for the errors in determining low surface areas.

All gases used must be free from moisture.

QUANTITY OF SAMPLE

A quantity of the test powder is accurately weighed such that the total surface of the sample is at least 1 m^2 when the adsorbate is nitrogen and 0.5 m^2 when the adsorbate is krypton.

Lower quantities of sample may be used after appropriate validation.

Measurements

Because the amount of gas adsorbed under a given pressure tends to increase when the temperature is decreased, adsorption measurements are usually made at a low temperature. Measurement is performed at 77.4 K, the boiling point of liquid nitrogen.

Method I: The Dynamic Flow Method

PRINCIPLE

In the dynamic flow method (see *Figure 1*), the recommended adsorbate gas is dry nitrogen or krypton, while helium is employed as a diluent gas, which is not adsorbed under the recommended conditions.

A minimum of three mixtures of the appropriate adsorbate gas with helium are required within the P/P_o range 0.05 to 0.30.

The gas detector-integrator should provide a signal that is approximately proportional to the volume of the gas passing through it under defined conditions of temperature and pressure. For this purpose, a thermal conductivity detector with an electronic integrator is one among various suitable types. A minimum of three data points within the recommended range of 0.05 to 0.30 for P/P_o is determined.

PROCEDURE

A known mixture of the gases, usually nitrogen and helium, is passed through a thermal conductivity cell, through the sample again, through the thermal conductivity cell, and then to a recording potentiometer.

The sample cell is immersed in liquid nitrogen, and the sample adsorbs nitrogen from the mobile phase. This unbalances the thermal conductivity cell, and a pulse is generated on a recorder chart.

The sample is removed from the coolant; this gives a desorption peak equal in area and in the opposite direction to the adsorption peak. Because this is better defined than the adsorption peak, it is the one used for the determination.

To effect the calibration, a known quantity of adsorbate, sufficient to give a peak of similar magnitude to the desorption peak, is injected into the system, and the proportion of gas volume per unit peak area is obtained.

A mixture of nitrogen and helium is used for a single-point determination; and several such mixtures or premixing two streams of gas are used for a multipoint determination.

The calculation is the same as the volumetric method.

Method II: The Volumetric Method

PRINCIPLE

In the volumetric method (see *Figure 2*), the recommended adsorbate gas is nitrogen, which is admitted into the evacuated space above the previously outgassed powder sample to give a defined equilibrium pressure, P, of the gas. The use of a diluent gas, such as helium, is therefore unnecessary, although helium may be employed for other purposes, such as to measure the dead volume.

Because only pure adsorbate gas, instead of a gas mixture, is employed, interfering effects of thermal diffusion are avoided in this method.

PROCEDURE

A small amount of dry nitrogen is admitted into the sample tube to prevent contamination of the clean surface, the sample tube is removed, a stopper is inserted, the tube is weighed, and the weight of the sample is calculated. Then the sample tube is attached to the volumetric apparatus. The sample is cautiously evacuated down to the specified pressure (e.g., between 2 Pa and 10 Pa). Alternately, some instruments are operated by evacuating to a defined rate of pressure change (e.g., less than 13 Pa/30 s) and by holding for a defined period of time before commencing the next step.

If the principle of operation of the instrument requires the determination of the dead volume in the sample tube, for example, by the admission of a nonadsorbed gas, such as helium, this procedure is carried out at this point, followed by evacuation of the sample. The determination of dead volume may be avoided using difference measurements: that is, by means of reference and sample tubes connected by a differential transducer. The adsorption of nitrogen gas is then measured as described below.

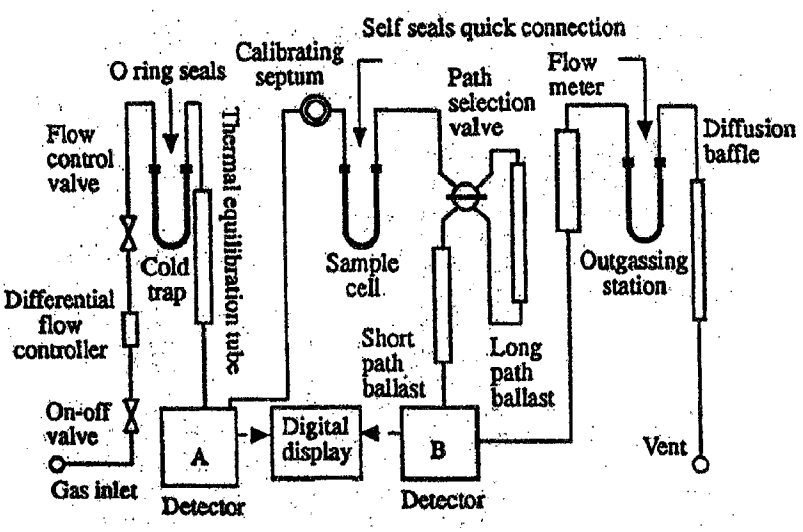

Fig. 1. Schematic diagram of the dynamic flow method apparatus.

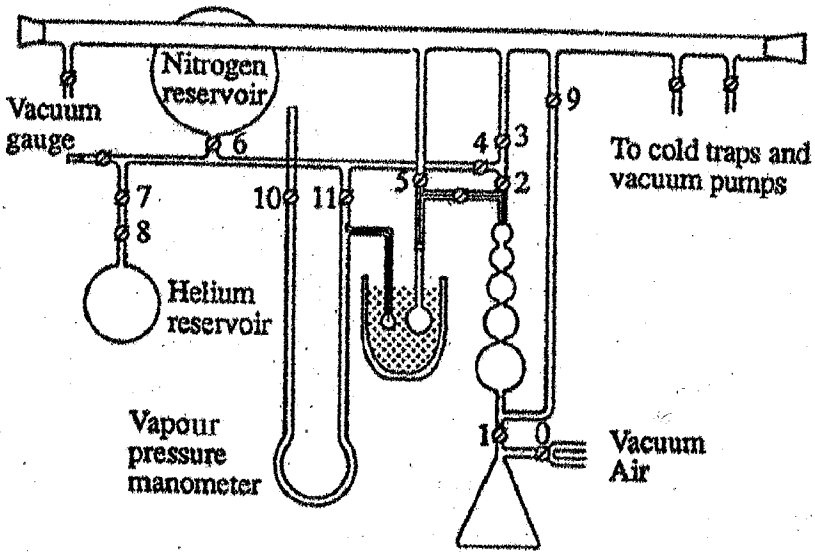

Fig. 2. Schematic diagram of the volumetric method apparatus.

Raise a Dewar vessel containing liquid nitrogen at 77.4 K up to a defined point on the sample cell. Admit a sufficient volume of adsorbate gas to give the lowest desired relative pressure. Measure the volume adsorbed, V_a. For multipoint measurements, repeat the measurement of V_a at successively higher P/P_o values. When nitrogen is used as the adsorbate gas, P/P_o values of 0.10, 0.20, and 0.30 are often suitable.

Reference Materials

Periodically verify the functioning of the apparatus using appropriate reference materials of known surface area that have a specific surface area similar to that of the sample to be examined.

⟨851⟩ SPECTROPHOTOMETRY AND LIGHT-SCATTERING

ULTRAVIOLET, VISIBLE, INFRARED, ATOMIC ABSORPTION, FLUORESCENCE, TURBIDIMETRY, NEPHELOMETRY, AND RAMAN MEASUREMENT

Absorption spectrophotometry is the measurement of an interaction between electromagnetic radiation and the molecules, or atoms, of a chemical substance. Techniques frequently employed in pharmaceutical analysis include UV, visible, IR, and atomic absorption spectroscopy. Spectrophotometric measurement in the visible region was formerly referred to as *colorimetry*; however, it is more precise to use the term "colorimetry" only when considering human perception of color.

Fluorescence spectrophotometry is the measurement of the emission of light from a chemical substance while it is being exposed to UV, visible, or other electromagnetic radiation. In general, the light emitted by a fluorescent solution is of maximum intensity at a wavelength longer than that of the exciting radiation, usually by some 20 to 30 nm.

Light-Scattering involves measurement of the light scattered because of submicroscopic optical density inhomogeneities of solutions and is useful in the determination of weight-average molecular weights of polydisperse systems in the molecular weight range from 1000 to several hundred million. Two such techniques utilized in pharmaceutical analysis are *turbidimetry* and *nephelometry*.

Raman spectroscopy (inelastic light-scattering) is a light-scattering process in which the specimen under examination is irradiated with intense monochromatic light (usually laser light) and the light scattered from the specimen is analyzed for frequency shifts.

The wavelength range available for these measurements extends from the short wavelengths of the UV through the IR. For convenience of reference, this spectral range is roughly divided into the UV (190 to 380 nm), the visible (380 to 780 nm), the near-IR (780 to 3000 nm), and the IR (2.5 to 40 μm or 4000 to 250 cm^{-1}).

COMPARATIVE UTILITY OF SPECTRAL RANGES

For many pharmaceutical substances, measurements can be made in the UV and visible regions of the spectrum with greater accuracy and sensitivity than in the near-IR and IR. When solutions are observed in 1-cm cells, concentrations of about 10 μg of the specimen per mL often will produce absorbances of 0.2 to 0.8 in the UV or the visible region. In the IR and near-IR, concentrations of 1 to 10 mg per mL and up to 100 mg per mL, respectively, may be needed to produce sufficient absorption; for these spectral ranges, cell lengths of from 0.01 mm to upwards of 3 mm are commonly used.

The UV and visible spectra of substances generally do not have a high degree of specificity. Nevertheless, they are highly suitable for quantitative assays, and for many substances they are useful as additional means of identification.

There has been increasing interest in the use of near-IR spectroscopy in pharmaceutical analysis, especially for rapid identification of large numbers of samples, and also for water determination.

The near-IR region is especially suitable for the determination of –OH and –NH groups, such as water in alcohol, –OH in the presence of amines, alcohols in hydrocarbons, and primary and secondary amines in the presence of tertiary amines.

The IR spectrum is unique for any given chemical compound with the exception of optical isomers, which have identical spectra. However, polymorphism may occasionally be responsible for a difference in the IR spectrum of a given compound in the solid state. Frequently, small differences in structure result in significant differences in the spectra. Because of the large number of maxima